REMARKS/ARGUMENTS

Claim Amendments

By present amendment claims 1-7 and 11-15 have been amended to remove non-elected subject matter, claims 24-29 have been withdrawn as being directed to non-elected subject matter, claims 30-31 have been cancelled without prejudice, claims 32 and 33 are re-presented claims 30 and 31, respectively, with the addition of the limitations of claim 25, and claims 34-35 are new. Support for the amendments is either apparent, or is as described hereinbelow.

The Applicants have amended claims 1-4 and 12 to enhance readability. Therefore, the "=" sign has been replaced with the word "is" and the definition for the variable "R_5" has been moved so that it appears after the definition for the variable "X". Further, the Applicants have amended claims 5-7 and 13-15 to clarify the nomenclature of the N-methylated compounds (i.e. those compounds where R_4 is CH_3). For these compounds, the Applicants have inserted the prefix "N" before the substituents attached to the nitrogen atom in keeping with the conventions of the International Union of Pure and Applied Chemistry (IUPAC). Also, claim 11 has been amended so that it is dependent on claim 1. The Applicants submit that these latter amendments to claims 1-4, 5-7 and 11-15 represent clarifying amendments only and in no way alter the scope of the amended claims.

Claims 1-16 and 32-35 are pending in this application.

The Official Action dated June 23, 2004 has been carefully considered. It is believed that the claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

The Invention

The present invention relates to the provision of new chiral compounds of Formula I and the use of the corresponding achiral, racemic and enantiomerically pure compounds of Formula I for the treatment of specific conditions in which cell death occurs by apoptosis. As stated on page 5, lines 23-24, of the application as filed, the compounds of Formula I which are optically pure are novel. Certain compounds of Formula I which are achiral are also novel. None of the compounds of Formula I, including the corresponding achiral, racemic and enantiomerically pure compounds, have been reported to prevent cell death by apoptosis, accordingly methods of treating conditions in which cell death occurs by apoptosis using achiral, racemic and enantiomerically pure compounds of Formula I are new.

Claim Objections

Election

The Applicants respectfully traverse the Examiner's asserted Restriction Requirement in the present invention as it relates to the group X. In particular, the Applicants traverse the requirement that when X is COOH, $COOR_5$ or tetrazole, the compounds of Formula I represent separate inventions and ask that these compounds and their compositions and methods of use be examined together.

The Applicants acknowledge that, 35 USC § 121 allows the Examiner to restrict claims to separate inventions, however, the MPEP 808.02 instructs the Examiner to assert a restriction under the following circumstances:

1) each distinct invention has a separate classification in the Patent Office patent classification system;
2) each distinct invention has a separate status in the art; or
3) a different field of search is necessary for each distinct invention.

If the Examiner's reason for asserting the Restriction Requirement relies on the "separate classification system" policy, the Requirement must clearly provide an

appropriate explanation as to why "each distinct subject has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search." Clearly the Examiner has not done this, in particular for compounds of Formula I where X is COOH, $COOR_5$ or tetrazole.

If the Examiner relies on each member of the Markush group as having acquired "a separate status in the art" then the MPEP instructs "[s]eparate status may be shown by citing patents which are evidence of such separate status." The Examiner has failed to cite any reference supporting a Restriction Requirement under (2) above, in particular for compounds of Formula I where X is COOH, $COOR_5$ or tetrazole.

If, however, the Examiner maintains that a different field of search is necessary for each member of the Markush group as in (3) above, then the Examiner's action suborns the purpose of describing the "metes and bounds" of an invention by circumscribing the subject matter in a synthetic genus. Under the Examiner's practice, each element of Markush groups will improperly encompass a separate invention. Clearly the Examiner has erred in asserting a Restriction Requirement in the present case for reason (3) above, in particular for compounds of Formula I where X is COOH, $COOR_5$ or tetrazole.

The Examiner's attention is drawn to the MPEP 808.02, concluding paragraph:

> Where, however, the classification is the same and the field of search is the same and there is no clear indication of separate future classification and field of search, no reasons, exist for dividing among related inventions.

In light of the above, the Applicants do not accept the asserted Restriction Requirement for Groups I, II and VI *pro forma*, but instead traverse the Examiner's action.

The Applicants have amended the claims so that they cover enantiomerically pure compounds of Formula I wherein X is COOH, $COOR_5$ or tetrazole, compositions comprising said compounds and methods of treating a particular disease described in claim 30 using said compounds, along with their racemic and achiral counterparts. It should be noted that claims 30 and 31 have been cancelled and re-presented as claims 32 and 33, respectively, containing the limitations of claim 25, upon which claims 30 and 31 were dependent.

Multiple Dependency

The Examiner has objected to claims 11 and 12 under 37 CFR §1.75(c) as being in improper form since a multiply dependent claim cannot depend on another multiply dependent claim. The Examiner contends that claims 11 and 12 depend on claims 3-9, of which claim 6 is a multiply dependent claim. It appears that the Examiner is not referring to the correct set of claims that were previously of record for the present application. In the claims previously on file (i.e. those corresponding to the claims as published in the International Preliminary Examination Report and as amended in the Preliminary Amendment filed on September 26, 2000) claim 11 is an independent claim and claim 12 depends only on claim 11. Further, claim 6 is not a multiply dependent claim. Clarification is requested.

35 USC §112, First Paragraph

The Examiner has objected to claims 25-31 under 35 USC §112, First Paragraph as the Examiner contends that the embodiment of a method for the prevention of a disease in which cell death occurs by apoptosis is not enabled in the disclosure as filed.

While not agreeing with the Examiner's position, to expedite examination of the present application, the Applicants have re-presented claims 30 and 31 in new claims 32 and 33, respectfully, in which the term "or prevention" has been removed. Claims 25-29 have been withdrawn as being directed to non-elected subject matter, however, it

should be noted that withdrawn claim 25, and accordingly withdrawn claims 26-29 dependent thereon, have also been amended to remove the term "or prevention".

In light of the above amendments, the Applicants respectfully request that the Examiner's objections to claims 25-31 under 35 USC §112, First Paragraph, be withdrawn.

The Examiner has also objected to claims 25-31 under 35 USC §112, First Paragraph, alleging that "the specification, while being enabling for the treatment of some disease in which cell death occurs by apoptosis using some compounds, *does not reasonably provide enablement for the treatment of <u>any disease</u> in which cell death occurs by apoptosis using <u>other</u> compounds embraced by the same claims*" (emphasis in original). In the present amendment, claims 25-29 have been withdrawn as being directed to non-elected subject matter. Claims 30 and 31 have been cancelled and represented as independent claims 32 and 33, respectively, with all of the limitations of claim 25. The Applicants respectfully traverse the Examiner's objection to claims 30 and 31 for the reasons that follow.

The Examiner sets out his objections under four headings, the response to each of which is provided below in the order in which they appear in the Office Action.

The Nature of the invention

The Examiner alleges that "[it] is very unlikely that substances with a considerable difference in their structure and with a variety of functional groups would all be effective in the same treatment". The Applicants submit that the compounds of the invention do not possess a "considerable difference in structure" and that the core structure represented by Formula I represents a patentable generic scaffold. Compounds of Formula I where X is COOH or $COOR_5$ (where R_5 is C_{1-5}alkyl) are related as acids and esters and in fact, the present Applicants have shown that the ester is converted *in vivo* (in the rat) into the corresponding acid, thus behaving as a

prodrug. Further, it is well known to those skilled in the art that a tetrazole group is a bioisostere of a COOH.

Accordingly, the Applicants submit that the Examiner's allegation that the claimed substances have considerable difference in their structure and with a wide variety of functional groups is in error.

The State of the prior art and the predictability or lack thereof in the art

The Examiner alleges that there is no absolute predictability which compounds of Formula I will exhibit the desired biological activity stating that there are some data *in vitro* supporting enablement for some compounds but not for others. The Applicants submit that in Tables 1-2 provided on pages 18 and 19 of the application as filed, the majority of the compounds of Formula I where X is COOH, $COOR_5$ or tetrazole possess cellular rescue activity. The exceptions are certain instances where one enantiomer of a specific compound is active where the other is not. The fact that the R and/or S enantiomer of the chiral compounds of Formula I may be more or less active than the other, does not render the activity of the racemic forms unpredictable. With respect to the lack of activity for some of the achiral compounds of the present invention, the Applicants submit that this may in fact be due to the vulnerability of bioassays to occasional often unexpected glitches. This fact is supported by the fact that *in vivo* screening performed on some of these compounds subsequent to filing has shown that some compounds previously indicated as non-rescuers in the *in vitro* screen do indeed have cellular rescue activity. This data has been provided in the attached declaration submitted under 37 CFR §1.132 .The Examiner is directed in particular to the activity of R-3-(2-pentylamino)propionic acid, which was indicated to be inactive in the *in vitro* screen, yet, showed rescue activity in the *in vivo* model. The Applicants further wish to point out that the *in vivo* screen also shows that R-4-(2-heptylamino)butanoic acid, a compound not specifically disclosed in the present application, but within the scope of the claims and representing an example of a compound where n = 3, was shown to have cellular rescue activity.

The Applicants submit, therefore that the data presented in the present application and in data submitted in the declaration herewith, support the predictability of the activity for all of the compounds as covered in amended claims 32-37 submitted herewith.

The breadth of the claims

The Examiner comments that the Applicants claim a method for the treatment of any disease in which cell death occurs by apoptosis using a compound of Formula I. The Examiner objects that the said method would include conditions that may be related to cell death by apoptosis in the future, without not even being tested. While not agreeing with the Examiner's comments, the Applicants have cancelled claims 25-29 directed to a method of treatment of a disease in which cell death occurs by apoptosis but has retained claims to a method of treating those specific diseases listed in previous claims 30 and 31 (now re-presented as claims 32 and 33).

The Examiner further comments that there are many organic compounds that would satisfy the limitations of Formula I. The Applicants object to this generic statement as a grounds for rejection under 35 USC §112, First Paragraph. For the reasons provided above, the Applicants submit that the data presented in the present application and in data obtained subsequent to filing and submitted in the declaration provided herewith, support the predictability of the activity for all of the compounds as covered in amended claims 32-37 submitted herewith. The fact that a large number of compounds may be covered within one synthetic genus is not a valid reason to reject a claim. The requirements for enablement are that an Applicant teach a person skilled in the art how to make and use the claimed invention. For the reasons provided above, the Applicants submit that they have met these requirements.

Examples provided in the specification

The Examiner has noted that the Table on page 18 of the application as filed demonstrates the effectiveness of some carboxylic acids derivatives in the said method of treatment, however some of the results indicate that there is no rescue indicating that some of the compound of Formula I are not active in said treatment.

An explanation for the activity, or purported lack of activity, for the compounds of Formula I as claimed in the present set of claims has been provided above. As such, the Applicants submit that the Applicants' invention as claimed in amended claims 32-37 submitted herewith, has been enabled throughout its entire scope.

In light of the above, the Applicants request that the Examiner's objection to claims 25-31 under 35 USC §112, First Paragraph, be withdrawn.

The Examiner has objected to claims 3-6, 16 and 25 under 35 USC §112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regards as the invention.

The Examiner notes that claims 3 and 4 include a limitation with respect to the chirality of the claimed compounds, however there is no indication as to the location of the chiral carbon. Further, since the Examiner notes that the chiral carbon is the one where R_1, R_2 and R_3 are connected, the definition of the compound includes instances where said carbon atom may have two substituents that are the same, and therefore be achiral.

In response the Applicants have amended claim 1, and accordingly claims 3 and 4 dependent thereon, to clarify that the compounds being claimed are limited to those where "R_1, R_2 and R_3 are each different so that the carbon atom to which they are attached is chiral", which overcomes the Examiner's objection.

The Applicants are confused by the Examiner's objections to claims 5, 6 and 11 as outlined on pages 8 and 9 of the Office Action. The Examiner appears to be reviewing the claims 5, 6 and 11 as filed in the corresponding PCT patent application as opposed to the claims as published in the International Preliminary Examination Report and as amended in the Preliminary Amendment filed on September 26, 2000. The Applicants submit that the correct and current versions of claims 5, 6 and 11 are those submitted herewith and that the objections raised by the Examiner on pages 8 and 9 of the Office Action do not apply to these claims. Clarification is requested.

The Examiner has objected to claim 25 as being indefinite in the term "A method for the treatment or prevention of a disease in which cell death occurs by apoptosis". The Examiner alleges that this is a "reach through" claim and further objects to the word "prevention". By the present amendment, claim 25 has been withdrawn from consideration since it is directed to non-elected subject matter, however the Applicants note that claim 25 has been currently amended to remove the term "or prevention".

In light of the above, the Applicants request that the Examiner's objections to claims 3-6, 16 and 25 under 35 USC §112, Second Paragraph, be withdrawn.

35 USC §102(b)

The Examiner has objected to compound and composition claims 1, 2, 5, 9-12 and 13-14 under 35 USC §102(b) as allegedly being anticipated by a number of prior art reference. The Applicants have amended the compound and compositions claims of the present application so it is more clear that they are intended to cover the only enantiomeric forms of the chiral compounds represented by Formula I.

The prior art cited on pages 10-11 of the Office Action discloses only racemates and achiral compounds, but no enantiomeric compounds. Furthermore, none of the compounds disclosed in the prior art references discovered by the electronic search (results appended to the Office Action) are enantiomers. In addition, none of the

previously disclosed compounds, compositions or methods in the cited references relates in any way to the use of any of compounds (enantiomers, racemates or achirals) in the treatment of any disease in which cell death occurs by apoptosis. A few achiral compounds not found in the prior art are protected by articulation in claim 7

In light of the above, the Applicants submit that all of the compounds and compositions encompassed by claims 1, 2, 5, 9-12 and 13-14 are novel and request that the Examiner's objection to claims 1, 2, 5, 9-12 and 13-14 under 35 U.S.C. §102(b) be withdrawn.

In view of the foregoing comments and amendments, we respectfully submit that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, the Examiner is kindly requested to contact the undersigned by telephone at (416) 957-1683 at the Examiner's convenience.

Respectfully submitted,

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